REMARKS

Upon entry of this amendment, claims 1, 3, 6, 15, 17-18, 21, 23-25, 29-53 are pending in the instant application. Claims 2, 4-5, 7-14, 16, 19-20, 22, and 26-28 have been cancelled herein, without prejudice or disclaimer. Claims 1, 3, 6, 15, 17-18, and 24-25 have been amended. Claims 33-53 have been withdrawn. Applicants reserve the right to prosecute the cancelled and withdrawn subject matter, as well as the originally presented claims, in continuing applications. Support for the amendments to claims 1, 3, 6, 15, 17-18, and 24-25 is at least found at page 4, lines 11-17 and page 6, lines 16-19. Accordingly, no new matter is added.

I. Specification

The Examiner has requested that Applicants correct the spelling of the word "propranolol" in the specification. *See*, Office Action, page 2, item 3. Accordingly, Applicants have made the appropriate corrections throughout the specification. See, Amendments to the Specification items 1-10. Applicants corrected additional typographical errors in Amendments to the Specification items 11-12.

II. § 112, first paragraph Rejections

Claims 1-4, 6, 7-8, 15, 17, 18, 20-21, 23-26 and 29-32 have been rejected under 35 U.S.C. 112, first paragraph, because the Examiner states:

> the specification while being enabling for "treating cardiotoxicity or hypertension induced by a vascular targeting agent selected from the group consisting of a combretastatin, a combretastatin A-4 phosphate, a combretastatin A-1 diphosphate and a pharmaceutically acceptable salt thereof" with the administration of said vascular targeting agent in combination with the specific beta-blocker or vasodilator (e.g., nitroglycerin and propranolol), does not reasonably provide enablement for "a treatment of a disease associated with vascular targeting", "vascular targeting agent", "an anti-hypertensive agent", "a combretastatin analog", and "neoplastic disease". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. *See*, Office Action, page 3.

Claims 2, 4, 7-8, 20, and 26 have been canceled and thus, the rejection is moot as applied to these claims. Accordingly, Applicants have amended claim 1 to the subject matter which the Examiner had indicated is enabled. Applicants submit that the rejection is moot as applied to

amended claim 1 and to the corresponding dependent claims 3, 6, 15, 17-18, 21, 23-25, and 29-32 and respectively request withdrawal of the rejection.

III. § 102 Rejections

Claims 1-4, 6, 7-8, 17, 26, and 29-31 have been rejected under 35 U.S.C. 102(a) or (e) as being anticipated by Curwen et al. US 2003/0144298 ("Curwen"). Applicants submit that the claims as-amended are not anticipated by Curwen.

The Examiner states that Curwen teaches a pharmaceutical composition or kit comprising a combination of antihypertensive agent, such as nitroglycerine, and an anti-angiogenic agent such as combretastatin A4, that is useful for the treatment of a disease state associated with angiogenesis including cancer in a warm-blooded mammal. *See*, Office Action, page 11.

Applicants have amended the claims to reflect the subject matter that the Examiner has said is enabled by the specification. *See*, Office Action, page 3. Applicants submit that the claims as-amended are not anticipated by Curwen. As amended, the claims of the instant application relate to a method of treating both cardiotoxicity and hypertension induced by a vascular targeting agent comprising administering said vascular targeting agent in combination with an anti-hypertensive agent to a mammal, wherein the vascular targeting agent is selected from the group consisting of combretastatin, combretastatin A-4 phosphate, combretastatin A-1 disphosphate, or a pharmaceutical acceptable salt, and further wherein said anti-hypertensive agent is a vasodilator. Support for the amended claims is found at least at page 4, lines 11-17 and page 6, lines 16-19.

Curwen does not anticipate the claims as-amended of the instant application because Curwen does not teach administering the combination of a vascular targeting agent and a vasodilator for the treatment of both hypertension and cardiotoxicity induced by the vascular targeting agent. But rather, Curwen teaches a method for the treatment of a disease state associated with angiogenesis, the process of forming new blood vessels, including disease states such as cancer, diabetes, psoriasis, rheumatoid arthritis, etc. by administering the combination. *See*, paragraphs [001]-[002] of Curwen. Further, Curwen relates to ways in which an antiangiogenic effect may be produced in a warm-blooded animal without causing hypertension. *See*, paragraph [0012] of Curwen. However, Curwen does not teach the use of the combination for the treatment of cardiotoxicity. Because Curwen does not teach using the combination for

the treatment of both cardiotoxicity and hypertension induced by a vascular targeting agent, Applicants submit that Curwen does not anticipate the amended claims of the instant invention and request withdrawal of the rejection.

III. § 103 Rejections

Claims 15, 18, 20-21, 23-25 and 32 have been rejected under 35 U.S.C. 103(a) as being upatentable over Curwen and further in view of Pettit et al., WO 99/35150 ("Pettit") and Pero, et al., U.S. Patent 6,773,702 ("Pero"). Applicants traverse the rejection.

It is well recognized under U.S. law, that any rejection of a claim for obviousness over a combination of prior art references must establish that: (1) the combination produces that claimed invention; (2) there is a reason to combine the prior art references in such a way to achieve the claimed invention; and (3) the prior art reveals that in so making or carrying out the claimed invention, those of ordinary skill would have a reasonable expectation of success. In re Vaeck, 947 F.2d 488 (Fed. Cir. 1991).

Applicants submit that a prima facie case of obviousness has not been established, because the first requirement is not met i.e., the combination does not produce the invention as claimed. Withdrawal of the rejection is requested.

Combination does not produce the claimed invention

Curwen discloses a method for the treatment of a disease state associated with angiogenesis, including disease states such as cancer, diabetes, psoriasis, rheumatoid arthritis, etc. by administering an anti-angiogenic agent and an anti-hypertensive agent. *See*, paragraphs [001]-[002] of Curwen. Curwen further relates to ways in which an anti-angiogenic effect may be produced in a warm-blooded animal without causing hypertension. *See*, paragraph [0012] of Curwen.

Pero teaches a method of treating cancer, specifically a method of counteracting tumor-induced immunosuppression by administering an effective low dose amount of combretastatin or a prodrug thereof, effective to permit tumor regression but that does not cause vascular shut down. Pero does not teach a method treating of cardiotoxicity induced by the administration of a vascular targeting agent.

Pettit discloses combretastatin prodrugs and their use to treat neoplastic disease. Pettit specifically focuses on methods of synthesis, including the chemistry of forming phosphate salt to improve water solubility. There is nothing in Pettit which teaches administering a combretastatin prodrug in combination with an anti-hypertensive agent in order to treat cardiotoxicity induced by a combretastatin prodrug.

The combination of Curwen in view of Pero and Pettit does not produce the claimed invention. The claimed invention relates to the unexpected result that anti-hypertensive agents can protect against the acute and transient cardiotoxicity that is associated with the shutdown of blood supply to a tumor induced by a vascular targeting agent. Specifically, the claimed invention is a method of treating both the cardiotoxicity and hypertension effect induced by a vascular targeting agent by administering the combination of a vascular targeting agent and vasodilator. Unlike the claimed invention, Curwen does not teach the treatment of both cardiotoxicity and hypertension. Pero and Pettit do not cure the deficiencies of Curwen. Thus, Applicants submit that the combination of Curwen, Pero and Pettit does not produce the claimed invention.

For the foregoing reasons, the combination does not produce the claimed invention and thus, the first requirement for establishing a prima facie case of obviousness has not been met. As such, Applicants submit that the rejection should be withdrawn.

CONCLUSION

On the basis of the foregoing, Applicants respectfully request that the rejection of the pending claims be withdrawn. If there are any questions regarding these remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

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